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Letter to the Editor

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Using "big data" to describe the effect of seasonal variation in thyroid-stimulating hormone

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To the Editor,

Defining reference ranges for use in laboratory medicine may be complicated by biological or clinical factors. For example, it is generally accepted that normative ranges for measures of thyroid-stimulating hormone (TSH) secretion are influenced by factors such as ethnicity, age, gender, body mass index, smoking status, circadian rhythm, dietary iodine intake, and autoimmune diseases [1]. Comparatively, there is less unanimity in the conclusions from studies investigating whether seasonal fluctuations of circulating levels of TSH represent a significant independent source of variability and should be accounted for. Indeed, some studies claim that seasonality does not affect TSH concentrations, probably because the amplitude of the circannual rhythm is smaller than the circadian variation [2]. Others show a significant yearly variation with the peak occurring in winter and trough in summer [1, 3]. They relate seasonal variation either to prolonged exposure to cold or to changes in ambient temperature or photoperiod. In consequence, these studies are suggestive for the fact that conventional population-based reference intervals may not correctly identify seasonal alterations in TSH secretion in individual subjects. A recent longitudinal study confirmed these older studies often conducted on a rather small number of individuals [4]. It concluded that the effect of the test season on the TSH secretion and the use of a fixed upper reference limit may impact the relative prevalence of subclinical hypothyroidism and euthyroidism. Therefore, the study advocated to consider seasonal variations before deciding on treatment of subclinical hypothyroidism, particularly in areas with a wide annual temperature. The strength of this study was its multiyear duration, use of a large cohort of healthcare recipients, and a single analytic method for measurement of TSH to exclude inter-assay variation as source of variation in the measurement [4].

Here we present an alternative concept that also gives evidence on seasonal fluctuations in TSH concentrations. It uses laboratory data obtained from our recently developed quality management web tool called the "Percentiler" [5]. In short, the application daily collects instrument-specific medians from TSH results preferably generated from analysis of outpatients' samples. The medians are sent electronically from all over the world to our database. We offer participating laboratories a freely accessible (by a laboratory-specific password) user interface that shows them the course of the moving median in time for each of their instruments and their peer. This free of charge application provides the participants with a quality indicator for stability of performance [5]. As shown in Figure 1, the Percentiler also visualizes seasonal changes in TSH concentrations. Indeed, the moving median of three laboratories from three different countries over a time period of 1-year peaks in winter time and drops in the summer with an absolute difference of more than 10%–15%, which is comparable to the peak-trough

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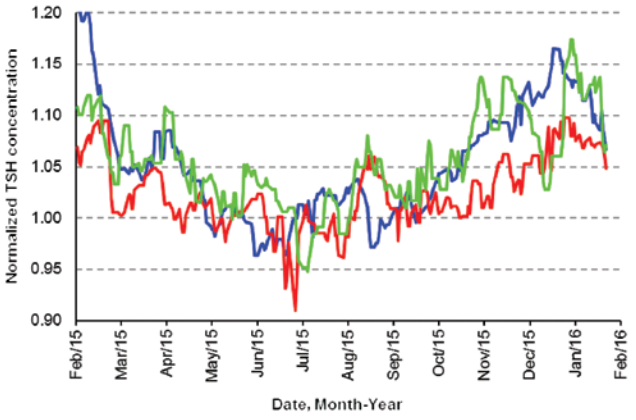

Figure 1: Time course of normalized TSH medians showing the effect of seasonality.
The colored lines represent the moving median of daily patient medians (grouped per 8 days) from three different laboratories (red, British; blue, Belgian; green, Japanese laboratory). The data span the period starting with February 1, 2015, and ending on January 31, 2016. The respective data were normalized to the summer values (June to August 2015) of the laboratory with the lowest TSH median values.

difference reported in a previous study [1]. To assure the reliability of the observation, we verified the IQC data of the concerned laboratories and found them stable. Note that in each of the laboratories, the daily medians are calculated from the results of a high number of patients (at least 500). We normalized the TSH data for the different laboratories to the summer values (June to August 2015) of the laboratory with the lowest long-term median. For information, the actual summer medians were (ranked according to increasing magnitude) 1.132, 1.372, and 1.692 mIU/L for the Belgian, Japanese, and British laboratory, respectively. These differences can, in part, be explained by the use of different platforms, i.e. the Abbott-Architect (Abbott Park, IL, USA), Roche-Cobas ElecSys (Mannheim, Germany), and Siemens-Centaur (Tarrytown, NY, USA), respectively. Also, the variation in patient populations might have an effect, i.e. the Belgian and British laboratories supplied for this study exclusively data from patient samples received from general practitioners, while the Japanese laboratory provided data mainly from patients consulting a doctor affiliated to a big hospital. One might wonder whether the seasonal variation pattern is also observed for the median of the entire peer group to which the above-mentioned laboratories belong. If this would be the case, it could be interesting to investigate whether the pattern is also present in the other peer groups of the Percentiler or is missing in some. However, in this stage of the project, it is not yet possible to verify this; some peer groups are not yet sufficiently substantiated and/or are too heterogeneous in terms of the laboratories' size. Indeed, in certain peer groups, laboratories perform only a low number of measurements per day, which leads to a rather high population variation that might mask the seasonal variation.

In conclusion, we demonstrated the potential of the Percentiler to address – from laboratory data generated worldwide – seasonal variations not only for TSH, but also for other analytes. This functionality can serve as an alternative and elegant approach to support the evidence of other longitudinal studies. It can also help the laboratory community to decide whether the observed fluctuations should be accounted for in diagnosis and evaluation of the adequacy of a therapeutic dose, and may require follow-up tests before deciding on treatment. Note, however, to fully exploit the potential of the Percentiler for observations as the one described here, preferably data from big-sized laboratories with proven stable analytical performance and low population variation should be used.

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